Remarks

Amendments to the Claims

Claim 1 has been amended to recite detection of "a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus encoded expression product" in place of "an expression product of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus." The specification supports this amendment at page 2, lines 19-20: "The HML-2 expression product which is detected is either a mRNA transcript or a polypeptide translated from such a transcript." Page 2, lines 19-20. The amendment merely clarifies the claim.

Claim 1 has also been amended to recite detecting "increased levels" of the HML-2 retrovirus encoded expression product in a patient sample "relative to a negative control sample" in place of detecting "the presence or absence" of the HML-2 expression product in the patient sample. The specification supports this amendment at page 24, lines 13-14: "Higher levels of expression product relative to a negative control indicate that the patient from whom the sample was taken has, for example, prostate cancer."

Claim 1 has further been amended to recite the patient sample is a "prostate or blood sample." The amendment is supported by the specification which discloses, "In general, therefore, the patient sample is tissue sample (*e.g.*, a biopsy), preferably, a prostate sample (*e.g.*, a biopsy) or a blood sample." Page 3, lines 7-8. The amendment is also supported by originally filed claim 3 which had recited that the patient sample was a prostate or blood sample.

None of these amendments adds new matter. The amendments also do not require further search or consideration. These amendments were not earlier made because applicants believed that the amendments and comments filed in the response to the Office Action dated March 10,

2004 were sufficient to overcome the rejections. Applicants also believe these amendments place the claims in condition for allowance.

Applicants respectfully request entry of these amendments.

The Rejection of Claims 1-3 and 8-15 Under 35 U.S.C. § 112, second paragraph

Claims 1-3 and 8-15 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 8 and 12 were canceled in applicants' amendment filed August 4, 2004. Claim 11 is canceled in the present amendment. Applicants respectfully traverse the rejection of independent claim 1 and dependent claims 2, 3, 9, 10, and 13-15.

A claim is definite if those skilled in the art would understand the scope of a claim when the claim is read in light of the specification. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571 (Fed. Cir. 1993); *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1993).

The Office Action asserts that the term "human endogenous MMTV-like subgroup 2 (HML-2)" is indefinite because it does not identify a structure required for diagnosis of prostate cancer. Office Action at page 2, lines 16-17. One of skill in the art, however, would understand the scope of HML-2 as recited in the rejected claims.

At the time of the effective filing date of the application, December 7, 2000, HML-2 was a well known family of retroviruses to those of skill in the art. The specification discloses, "Because HML-2 is a well-recognized family, the skilled person will be able to determine without difficulty whether any particular endogenous retroviruses is or is not a HML-2." Page 37, lines 11-12. Thus, being well aware of the structure of members of the HML-2 family of

retroviruses, one of skill in the art would have been able to determine the scope of the genus of HML-2.

Applicants respectfully request withdrawal of this rejection.

The Rejections of Claims 1-3, 9-11, and 13-15 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 9-11, and 13-15 stand rejected under 35 U.S.C. § 112, first paragraph, as insufficiently described. Claim 11 has been canceled. Applicants respectfully traverse the rejection of independent claim 1 and dependent claims 2, 3, 9, 10, and 13-15.

Claim 1 is directed to a method for diagnosing prostate cancer. The method comprises a step of detecting increased levels of a HML-2 retrovirus encoded expression product in a patient prostate or blood sample relative to a negative control sample.

To determine whether the claims are in compliance with the written description requirement, the Patent Office must first construe the claims. M.P.E.P. § 2163 (II) (A) (1). Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. *In re Morris*, 127 F.3d 1048 (Fed. Cir. 1997). A particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment. *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870 (Fed. Cir. 2004).

In rejecting claims 1-3, 9-11, and 13-15 the Patent Office has construed the recitation in claim 1 of an "expression product of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus" as reading on an expression product of a HML-2 retrovirus or any polynucleotide having at least 75% sequence identity to SEQ ID NO: 150. The final Office Action alleges:

> The specification on page 37, lines 13-15 reads "'Preferred members of the HML-2 family for use in accordance with the present invention are those whose proviral genome has an LTR which as at least 75% sequence identity to SEQ ID NO: 150.' The claims are drawn to a method of diagnosing prostate cancer by detecting the presence of HML-2 or by having at least 75% sequence identity to the polynucleotide of SEQ ID NO: 150.

Final Office Action at page 3, lines 3-7. Applicants disagree with the Patent Office's construction of the claims. First, the construction is not reasonable, *i.e.*, the claims recite that the expression product is that of a HML-2 retrovirus while the Patent Office's construction does not necessarily read on an expression product of an HML-2 retrovirus. Second, the Patent Office has read a preferred embodiment appearing in the written description into the claim when the claim language may be broader than the embodiment; such a reading is not permissible. Nonetheless, applicants have amended claim 1 to clarify that the method step detects "a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus encoded expression product." The amendment makes clear that the expression product detected in the method is encoded by a HML-2 retrovirus and cannot be an expression product of <u>any</u> polynucleotide having at least 75% sequence identity to SEQ ID NO: 150.

Once it has construed the claims, the Patent Office must review the entire application to understand how the applicant provides support for the claimed invention including each element and/or step. M.P.E.P. § 2163 (II) (A) (2). Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

HML-2 retroviruses were well-known in the art at the time of the effective filing date of the application (December 7, 2000) and therefore need not be described in detail in the specification. The specification explicitly teaches: "Because HML-2 is a well-recognized

family, the skilled person will be able to determine without difficulty whether any particular endogenous retroviruses is or is not a HML-2." Page 37, lines 11-12. The specification supports its assertion that HML-2 retroviruses were known in the art prior to its December 7, 2000 effective filing date. The specification teaches that:

> HERV isolates which are members of the HML-2 subgroup include HERV-K10 [137, 142], the 27 HML-2 viruses shown in Figure 4 of reference 147, HERV-K(C7) [148], HERV-K(II) [145], HERV-K(CH). Table 11 provides a list of all known members of the HML-2 subgroup of the HERV-K family as determined by searching the Double-Twist database containing all genomic contigs with the sequence AF074086 using the Smith-Waterman algorithm with the default parameters: open gap penalty = -20 and extension penalty = -5.

Page 35, lines 16-22. The specification references 31 published HML-2 retrovirus sequences that were known in the art prior to December 7, 2000 and describes an additional 28 HML-2 retrovirus sequences in Table 11. The specification supports the genus of HML-2 retroviruses by referencing 59 HML-2 retrovirus sequences.

Because the sequences of HML-2 retroviruses were known in the art, their RNA and polypeptide expression products also are easily recognized. Nonetheless, the specification provides numerous examples of sequences of HML-2 expression products including:

- Examples of gag nucleotide sequences: SEQ IDs 7, 8, 9 & 11 [HERV-K(CH)]; SEQ ID 85 [HERV-K108]; SEQ ID 91 [HERV-K(C7)]; SEQ ID 97 [HERV-K(II)]; SEQ ID 102 [HERV-K10]. Page 16, lines 7-9.
- Examples of gag polypeptide sequences: SEQ IDs 46, 47, 48, 49, 56 & 57 [HERV-K(CH)]; SEQ ID 92 [HERV-K(C7)]; SEQ ID 98 [HERV-K(II)]; SEQ IDs 103 & 104 [HERV-K10]; SEQ ID 146 ['ERVK6']. Page 16, lines 10-12.
- Examples of prt nucleotide sequences: SEQ ID 86 [HERV-K(108)]; SEQ ID 99 [HERV-K(II)]; SEQ ID 105 [HERV-K10]. Page 16, lines 17-18.
- Examples of prt nucleotide sequences: SEQ ID 106 [HERV-K10]; SEQ ID 147 ['ERVK6']. Page 16, lines 19-20.

- Examples of pol nucleotide sequences: SEQ ID 87 [HERV-K(108)]; SEQ ID 93 [HERV-K(C7)]; SEQ ID 100 [HERV-K(II)]; SEQ ID 107 [HERV-K10]. Page 16, lines 24-25.
- Examples of pol polypeptide sequences: SEQ ID 94 [HERV-K(C7)]; SEQ ID 108 [HERV-K10]; SEQ ID 148 ['ERVK6']. Page 16, lines 26-27.
- Examples of env nucleotide sequences: SEQ ID 88 [HERV-K(108)]; SEQ ID 95 [HERV-K(C7)]; SEQ ID 149 ['ERVK6']. Page 17, lines 4-5.
- Examples of env polypeptide sequences: SEQ ID 96 [HERV-K(C7)]; SEQ ID 108 [HERV-K10]; SEQ ID 149 ['ERVK6']. Page 17, lines 6-7.
- Examples of cORF nucleotide sequences: SEQ ID 89 and SEQ ID 90 [HERV-K(108)]. Page 17, line 13.
- Examples of cORF polypeptide sequences at SEQ ID 109. Page 17, line 14.

Finally, the Patent Office must determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention as a whole at the time the application was filed. M.P.E.P. § 2163 (II) (A) (3). A description of a genus of may be achieved by means of a recitation of a representative number of members of the genus, defined by sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d at 1559 (Fed. Cir. 1997).

As discussed above, the specification describes that the sequence of 59 species of the genus of HML-2 retroviruses were known in the art at the time of the effective filing date of the application. The specification also discloses example sequences of at least 20 polynucleotide and 20 polypeptide expression products of the genus of HML-2 retrovirus encoded expression products. The specification, therefore, sufficiently describes the genus of HML-2 retroviruses and their encoded expression products by a disclosure of and/or reference to well-known sequences of a representative number of HML-2 genomes and HML-2 encoded expression

products. Thus, as a whole, the specification adequately describes the subject matter of claims 1-3, 9, 10, and 13-15.

In support of its position that the claims are not adequately described, the final Office Action cites Zsiros (*J. Gen. Vir. 79* (1998):61-70) as teaching that HML-2 comprises a group of retroelements having diverse structures. Office Action at page 3, lines 11-12. Zsiros teaches the identification of ten new HML-2 retroviruses in human cell samples. Zsiros teaches that "we identified ten new members of the HML-2 subgroup." Page 61, lines 14-15 of the abstract. Zsiros' ability to identify ten new HML-2 retroviruses provides further evidence that, prior to the effective filing date of the application, the members of the genus of HML-2 retroviruses were well-known in the art and could readily be identified by those of skill in the art. Therefore, Zsiros supports the specification's disclosure that the skilled person will be able to determine without difficulty whether any particular endogenous retrovirus is a HML-2 and the description of the claims.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 1-7, 9-11, and 13-15 Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 9-11, and 13-15 stand rejected under 35 U.S.C. § 112 first paragraph as not enabled. Claim 11 has been canceled. Applicants respectfully traverse the rejection of independent claim 1 and dependent claims 2-7, 9, 10, and 13-15.

Claim 1 is directed to a method for diagnosing prostate cancer. The method comprises a step of detecting increased levels of a HML-2 retrovirus encoded expression product in a patient prostate or blood sample relative to a negative control sample.

The enablement requirement sets forth that the specification must describe how to make and use the claimed invention. 35 U.S.C. § 112, ¶ 1. To satisfy the enablement requirement, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991).

In order to make an enablement rejection, the Patent Office has the initial burden to establish a reasonable basis to question why the scope of protection provided by a claim is not adequately enabled by the disclosure. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). It is incumbent upon the Patent Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. *In re Marzocchi*, 439 F.2d 220 (CCPA 1971).

The Office Action asserts that the claims are not enabled because they do not indicate a particular retrovirus that can be used to detect prostate cancer:

> The specification on page 37, lines 13-15 reads 'Preferred members of the HML-2 family for use in accordance with the present invention are those whose proviral genome has an LTR which has at least 75% sequence identity to SEQ ID NO: 150. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the myriad of nucleic acids and oligonucleotides.

Office Action at page 4, lines 5-10. As discussed in the response to the written description rejection above, at least 59 retroviruses of the HML-2 group and at least 40 of their RNA and polypeptide expression products were well known in the art at the December 7, 2000 priority

date of this application. Zsiros provides evidence that one of skill in the art would be able to identify and classify sequences as HML-2 retroviral sequences without having to resort to undue experimentation. Because HML-2 retroviral sequences were well-known in the art and would readily have been recognized, one of skill in the art would have been able to identify HML-2 retrovirus encoded expression products for detection without resorting to undue experimentation.

Claim 1 comprises a single step of detecting an increase in expression of HML-2 retrovirus encoded expression products in a patient blood or prostate sample relative to a negative control sample. The specification teaches one of skill in the art how to detect an HML-2 retrovirus encoded expression products. The specification teaches example methods of directly (page 9, line 27 to page 10, line 14) and indirectly (page 10, lines 15-22) detecting HML-2 encoded mRNA expression products. The specification also teaches hybridization conditions for an example method of directly detecting mRNA at page 12, lines 13-30. The specification further teaches example methods of directly (page 17, line 15 to page 18, line 22) and indirectly (page 18, lines 23-29) detecting the HML-2 encoded polypeptide expression products. The specification also teaches how to detect an increased level of HML-2 retrovirus encoded expression product in a patient prostate of blood sample relative to a negative control sample at page 24, line 7 to page 25, line 16. These teachings of the specification are sufficient to enable the claimed methods.

The final Office Action, however, asserts that the claims are not enabled because, "Applicants have not provided [a] sufficient teaching to show that all HML-2 variants are predictably associated with prostate cancer." Office Action at page 4, lines 12-13. The Patent Office does not explain why it doubts that all HML-2 variants will be predictably associated with prostate cancer. The Patent Office also offers no evidence or reasoning why it doubts applicants'

disclosure that all HML-2 variants will be predictably associated with prostate cancer. *In re Marzocchi* at 224.

The final Office Action also asserts that the claims are not enabled because: "Applicants have not provided [a] sufficient showing that an increase in the HML-2 level in the blood correlates with only prostate cancer." Final Office Action at page 4, lines 16-17, emphasis in original. First, the specification clearly defines "diagnosis" as encompassing a screening process: " 'diagnosis' according to the invention can range from a definite clinical diagnosis of disease to an indication that the patient should undergo further testing which may lead to a definite diagnosis. For example, the method of the invention can be used as part of a screening process, with positive samples being subjected to further analysis." Page 24, lines 16-19. Therefore, it is not necessary for increased expression of a HML-2 encoded product in blood to necessarily be associated with prostate cancer. It may simply warrant further testing. Second, none of the references cited in the final Office Action support the Patent Office's position that detection of HML-2 expression products in blood indicates pathologies of organs or tissues other than prostate.

The final Office Action cites Medstrand (*J. Virol. 67* (1993):6778-6787) as teaching that HML-2 can be detected in tissues such as placenta and kidney. The final Office Action then concludes that an increase in the level of HML-2 in the blood could be due to pathologies found in the kidney or placenta and not due to prostate cancer. Final Office Action at page 4, lines 17-20. Applicants agree that Medstrand teaches detection of HML-2 expression products in placenta and kidney. However, Medstrand does not teach that levels of HML-2 expression products in blood will increase as a result of a kidney or placenta pathology. The Patent Office also offers no support for its assertion that, merely because HML-2 expression is detected in

kidney and placenta, a kidney or placenta pathology will increase HML-2 encoded expression products in blood. Medstrand provides no relevant teaching that would cast doubt on the ability to diagnose prostate cancer by detecting increased levels of an HML-2 encoded expression product in blood relative to a negative control sample.

The final Office Action cites Andersson (*Aids Res. And Hum. Retroviruses 12* (1996): 833-840) as teaching that HML-2 is detected in the PBMCs of healthy donors and concludes that it would not be predictable whether the presence of HML-2 in blood would be indicative of prostate cancer because HML-2 is normally found in blood. Final Office Action at page 4, line 20 to page 5, line 1. Applicants have amended claim 1 to recite that the patient sample is compared to a negative control sample to account for any basal level of HML-2 encoded expression products in blood.

Finally, the final Office Action cites Yin (*Aids Res. and Hum. Retroviruses 13* (1997): 507-516) as teaching association of MMTV-like retroviruses with human breast cancer. The final Office Action then states, "Men are also susceptible to developing breast cancer, although rarely [see Perkins et al. BMJ, 2003]. Therefore, detection of HMML-2 [sic] in male tissue such as blood could not provide information regarding the status of the prostate in the patient." Final Office Action at page 5, lines 3-5. Applicants respectfully disagree. Yin teaches detection of HML-2 expression levels in breast tissue and placenta, but not blood. Page 510, column 2, lines 39-43. Therefore, Yin provides no evidence that HML-2 levels will be changed in blood as a result of breast cancer. In fact, Yin teaches that HML-2 expression is <u>not</u> significantly different in normal vs. cancerous breast tissue. "For the other five hml probes [hml-1, hml-2, hml-3, hml-5, and hml-6], no marked differences could be detected between human breast cancer and nonmalignant breast tissue in the patterns of the dot hybridization." Page 510, column 2, lines

47-51. Thus, Yin, if anything, supports applicants' position that increased levels of an HML-2 encoded expression product in blood will be due to prostate cancer, not to pathology of another organ or tissue.

The Patent Office fails to make a *prima facie* case that claims 2-7, 9, 10, and 13-15 are not enabled.

Applicants respectfully request withdrawal of the rejection.

Objection to Claim 11

Claim 11 is objected to as being of improper form for failing to further limit the subject matter of a previous claim. Claim 11 has been canceled to obviate the objection.

Applicants respectfully request withdrawal of the objection.

Respectfully submitted,
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